OBITUARY

R. B. Woodward, 1917–1979

THE sudden death of Robert Burns Woodward of Harvard University on 8 July 1979 at the age of 62, marked the passing of one of the most important organic chemists of this century.

In offering the following account of some aspects of Woodward's achievements the main scientific emphasis will be on his contribution to chemical syntheses. I will leave to others a discussion of the celebrated Woodward-Hoffmann rules. It would, however, be wrong to undertake this exegesis before giving some idea of Woodward's impact on those — and they were hundreds — who came in contact with him.

Woodward's impact on his associates came first from an awesome command of the whole of organic chemistry, ranging from the incredibly complex mass of interrelations and transformations which chemists had produced while unraveling the molecular architecture of complex natural products, such as quinine, morphine or strychnine; to the ever more rapidly accumulating data on the course of chemical reactions and their theoretical basis; extending finally to the multitude of transformations, not excluding the most obscure or esoteric, which might be put to use some day in the rational construction of a complex structure.

Woodward's great strength was his conviction, which he conveyed to his associates, that chemical problems should be placed in a rigorously rational framework; leaving no room for fuzziness, for half understood data, for any but the most mercilessly logical deduction, whether dealing with the structure determination of an unknown natural product, or of an intermediate in a synthetic sequence. Woodward's intense commitment to organic chemistry was allied to the conviction that there must be underlying order beneath what often seemed a chaotic mass of unrelated observations. This approach showed fruit very early (1941) in the well-known "Woodward rules" which provided a generally useful correlation of important structural features of α, β-unsaturated ketones with their ultraviolet absorption maxima.

This early recognition of the importance of the informed application of physical methods to structural problems led Woodward to give a major role to the emerging tool of infrared spectroscopy in his rigorous deduction of the β-lactam structure of penicillin (1944-45). This, and the later conclusion that the vast amount of the existing strychnine chemistry demanded revision of the accepted structure to a different one, now known to be correct, are early examples of Woodward's mastery of this highly intellectual form of detective work. His skill in presenting his conclusions in a dramatic and lucid style makes his accounts of the elucidation of the structures of strychnine and, *inter alia*, of the tetracyclines or tetrodotoxin fascinating and highly rewarding reading. This is true even today, in spite of the fact that such problems have largely been taken away from chemistry by advances in X-ray crystallography.

The faith in an underlying rational structure showed itself also in Woodward's brilliant use of the "curved arrows" which Robinson's genius had earlier introduced into organic chemistry, to indicate the breaking and forming of bonds, and which have become an essential conceptual tool in visualizing the path from reactants to products. It was Woodward, more than anyone else, not excluding Robinson himself, who showed that Robinson's curved arrows could be submitted to rigorous logical constraints, and that, when they were thus used, they would greatly assist, not only in systematizing observed reactions, but also in predicting which reaction might be possible, and which unlikely. An early example (1948; 1950) of Woodward's command of this tool can be found in his unraveling of some baffling molecular transformations in the Santonin series.

There is one area of chemistry which is most uniquely the domain of organic chemistry, and that is molecular architecture, or synthesis. As chemists entered the twentieth century, the very small number of reactions which might be useful in reaching the complex targets represented by natural products such as cocaine, quinine, morphine or the steroids, coupled with a general lack of knowledge of ways to control stereochemistry, the three dimensional arrangement of atoms in space, made the challenge of total synthesis of most natural products as formidable as it was exciting. Nevertheless, some beginnings were made: Willstätter synthesized tropinone, the parent of cocaine, around 1900. This was a work of genius, given the state of development of chemical synthesis at that time, but the labored nature of the synthesis also served to emphasize the enormous problems to be faced by would-be molecular architects.

It must have been as important psychologically as it was chemically startling, therefore, when Robert Robinson's famous construction of tropinone burst upon the chemical world in 1917. Willstätter then succeeded in transforming tropinone into cocaine in 1923: the possibility of other complex total syntheses could now be contemplated. Some progress on methodology came from "partial synthesis," the transformation of one natural product into another (e.g. ascorbic acid from hexoses by Haworth, and by Reichstein, in 1933); the forbidding, though achiral, haemin was put together by H. Fischer in 1928 by a combination of steps which must have convinced any would-be practitioner that witchcraft must play a large part in a successful synthesis. Probably the greatest achievements in the decade preceding the second World War were the synthesis of dihydroquinine by Paul Rabe in 1931, and that of equilenin by Bachmann in 1939.

It is on that stage that R. B. Woodward made his dramatic entrance with the announcement of the synthesis of quinine (with W. E. Doering) in 1944. The synthesis commanded worldwide atention because of the burst of publicity (front page of the *New York Times:* "Second Answer to Japan") (the first, being, supposedly, synthetic rubber) which propelled Woodward, then twenty-seven, to a limelight which he did not altogether dislike. Dramatic as it may have seemed to the press, Woodward's quinine synthesis closely followed the scheme laid out by Rabe in his hydroquinine synthesis. It shares with that early synthesis an almost total lack of sterochemical control. And yet, it is of great importance because, in connection with the construction of a piperidine derivative, it introduced what I believe to be one of Woodward's most important contributions to the strategy of complex synthesis: the formation, manipulation and eventual cleavage of rings of carbon atoms as a method of construction of acyclic elements. This approach led to a considerable simplification of the route to the target structure, since it allowed carrying

functional groups in a latent, less reactive form: in the piperidine precursor of quinine, an eventual ε-aminoheptanoic acid system is constructed by the cleavage of a 2-methylcyclohexanone, a chemically less reactive, and thus more easily controllable system.

The modern era of concern for stereochemistry started in the period 1950-1955, a period which saw the development of stereospecific, or highly stereoselective, syntheses of morphine, cantharidin, cortisone, cedrol and strychinine. These syntheses were all carried out without taking advantage of the enormous help, just becoming available, of Barton's principles of conformational analysis, but they are important because they represent the first successful efforts to take stereochemistry explicitly into account during the process of synthesis planning. This may seem an obvious prerequisite to a successful synthesis, but one need only read the highly imaginative, though largely inconclusive, series of some sixty papers on steroid "synthesis" by Robinson and his collaborators to see the staggering efforts which could be made to reach synthetic targets (steroids in this case), without any concern for the need to control the relative arrangement of the relevant atoms in space. When one considers that without such control, the connectivity implied by the two-dimensional structure of cholesterol represents 256 different substances, only one of which is cholesterol, it is no wonder that these efforts, brilliant as they sometimes were, remained largely abortive.

Although Woodward's 1951 steroid synthesis was only partially stereoselective in contrast to the cortisone synlthesis (by L. H. Sarett) referred to above, it was nevertheless highly influential because it against used the structural simplification made possible by a temporary ring: a cyclohexene ring serves as the source of the steroid D-ring via its cleavage and cyclization to a more functional cyclopentene aldehyde. One also sees here an illustration of another important principle of many Woodward syntheses: the carbon framework is constructed as rapidly as possible, leaving some function (e.g. double bond) which will allow eventual structural adjustments.

It is with the synthesis of strychnine, in 1954, that Woodward began a series of classically elegant syntheses which have not yet been surpassed. In addition to strychnine, they are those of reserpine (1956), of chlorophyll (1960) and of the "western half" of vitamin B_{12} (1972). In the strychnine construction, the ubiquitous ring element, placed in the α-position of the indole ring of tryptamine, is a dimethoxybenzene ring which is here a latent 1,4 butadienedicarboxylic (muconic) ester system, in a much less reactive form. Before that transformation, however, that same ring is brilliantly used to ensure that an intramolecular cyclization via an iminium salt occurs at the β-position of an indole ring. The synthetic use of a dimethoxybenzene ring as a precursor of a muconic acid illustrates an aspect of the Woodward mastery which has been referred to previously: the cleavage of an ortho-dimethoxybenzene to a muconic acid had been stored in Woodward's memory since he had noticed its use by Speyer in the degradation of codeine. He was able to recall it just when it would be most dramatically useful.

In the synthesis of strychnine, details of oxidation states were consciously held in the background because of the great structural simplification thus allowed in the construction of the framework. This approach is further refined in the next great synthesis, that of reserpine, in which full and impressive use is made, for the first time, of Barton's conformational principles. In that synthesis, we have, once again, the use of a cyclohexene ring as a surrogate for an eventual aldehydo-ester. We also see here the dramatic simplification produced by the use of a double bond as the precursor of the monomethyl ester of a 1,2-glycol. There were, *a priori*, four possible such systems which might result from the cyclohexene double bond. Woodward had acquired, by that time, extraordinary confidence in his ability to find some way to make molecules dance to his tune: he felt that something might well happen during the synthesis, which would solve this potentially vexing problem. He was not disappointed. Only someone with Woodward's ability to deduce structures from a combination of limited spectral data and mechanistic insight could possibly have capitalised on the remarkable chemical events which provided a solution to the problem. Seldom has it been more true that "chance favors the prepared mind."

Chlorophyll and the "western half" of vitamin B_{12} will end this broad sketch. In the synthesis of the former, it is still notable that a problem in producing the required regiochemistry was solved by selecting an aminoethyl group as precursor of an eventually required vinyl substituent, and using it in temporary ring formation with a pyrrole aldehyde. Again, the very difficult problem of introducing the two so-called "extra" hydrogens specifically in one of four pyrrole rings was solved, in a unique manner, by a sequence involving cyclization followed by cleavage.

Finally, when we come to the B_{12} synthesis of 1972, we are treated to a pyrotechnic display of appearing and disappearing rings which are ued here to achieve control of almost all the asymmetric centers in the molecule. A propionic acid chain arises from the remains of an anisole ring, and another one from a temporarily constructed cyclohexene. A δ-ketoacid originates from the cleavage of a cyclopentene; an aminoacid system is born from a cyclopentanone, as yet further rings make their tightly orchestrated entrances and exits from the B_{12} stage: a grand final tribute to the power of this approach to synthesis.

I referred at the very beginning to the great impact that Woodward had on all who associated with him. This was nowhere more obvious than in the celebrated "problem seminars" in which Woodward was always willing to take on all those who cared to match wits and deductive skills with him. It was not just the graduate students and postdoctoral associates who benefitted from contact with Woodward's logical approach to all chemical problems: an impressive number of papers by celebrated chemists all over the world (Arigoni, Bartlett, Barton, Bloch, Djerassi, Eschenmoser, Gates, Inhoffen, Jeger, Klyne, Prelog, Wilkinson, Winstein, Witkop. . .) have Woodward as a coauthor, obvious testimony to the insights that were gained by discussions with him.

Woodward would not have been human had he not enjoyed the attention he commanded. He relished keeping audiences enthralled for hours with a lecture in which he obviously savoured highlighting the already brilliant work he was describing by using meticulously drawn formulas, dramatically enhanced by the controlled use of colored chalk, further to emphasize the image of one in total command of his environment. He was not above playing along with the sensationalism of the media: "That is what the public wants of its heroes"; and he had no doubt that he had earned the right to special recognition at every level. One anecdote, perhaps, sums up the view he had of his rightful place in the world: A new guard at Harvard had just told Woodward that his (blue) car could not be left where he had placed it. "Why is that?" said Woodward. "Your name is not on the list," said the guard. "It isn't?" said Woodward, turning back toward the guard without stopping, "well . . . put it there!" One thing is certain, Woodward's place in chemical history is permanently reserved.

Gilbert Stork

G.S. Forbes

GEORGE SHANNON FORBES, Emeritus Professor of Chemistry at Harvard University, died on 24 June 1979 in his home in Cambridge, Massachusetts.

Born on 17 March 1882 in Boston, Massachusetts, Forbes' interest in science was awakened at the age of eight, by a lecture on pendulums given by his father, George Fairfield Forbes, who was a pioneering teacher of experimental science at the prestigious Roxbury Latin School. But when young Forbes graduated from that same school he aspired to a career as a professor of classics. During his sophomore year at Harvard College, he reports, in a course on qualitative analysis the